Tetrahedron Letters 55 (2014) 3249–3251

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Copper powder-catalyzed N-arylation of imidazoles in water using 2-(hydrazinecarbonyl)pyridine *N*-oxides as the new ligands

Feng-Tian Wu, Nan-Nan Yan, Ping Liu, Jian-Wei Xie *, Yan Liu, Bin Dai

*School of Chemistry and Chemical Engineering/The Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan, Shihezi University, North 4th Road, Shihezi 832003, China*

ARTICLE INFO

*Article history:*
Received 29 January 2014
Revised 2 April 2014
Accepted 10 April 2014
Available online 23 April 2014

*Keywords:*
Copper powder
*N,O*-Ligand
N-arylation
Cross-coupling
Water-chemistry

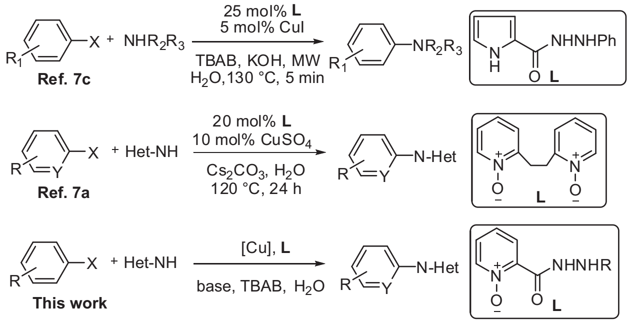
ABSTRACT

2-(2-Hydrazinecarbonyl)pyridine *N*-oxides, which were derived from pyrrole-2-carbohydrazides and pyridine *N*-oxides, were synthesized and utilized as the ligands for copper powder-catalyzed N-arylation of imidazoles with aryl halides in water. Imidazoles could be arylated smoothly with various aryl halides to provide the title products in preferable yields without the need of an inert atmosphere.

*N*-Arylimidazoles are common and useful motifs in medicinal, biological, and material sciences.[1] The traditional method for the preparation of these moieties is via $S_NAr$ substitution of imidazoles with activated aryl halides or the classic Ullmann-type coupling reaction.[2] However, the drawbacks of these methods are the use of stoichiometric amounts of copper reagents and high reaction temperatures. Fortunately, some *N*- and *O*-based ligands were found to facilitate the copper-catalyzed C–N coupling reactions by Buchwald et al.[3] and Taillefer et al.,[4] respectively. Thereafter, a series of practical ligands, including monodentate and bidentate ones, have been developed to expedite the Ullmann-type C–N formation.[5]

Recently, water has emerged as a highly desirable solvent for organic transformations in terms of cost, safety, availability, and environmental concerns,[6] of which the copper-based amination of aryl halides in water have also attracted much attention.[7] Among them, Wan and co-workers reported a typical copper-catalyzed C–N coupling in water with utilization of pyrrole-2-carbohydrazides as ligands.[7c] However, probably because of the poor water-soluble and unstable nature of the ligand, the relatively high molar ratio (5:1) of ligand and copper was needed. At the same time, Zhou and co-workers[7a] reported pyridine *N*-oxide could efficiently promote Cu-catalyzed N-arylation of imidazoles in water, and superior solubility of the ligand maybe played an essential role. Therefore, we reasonably assume that 2-(hydrazinecarbonyl)-pyridine *N*-oxides, which replaced pyrrole ring with pyridine *N*-oxide, might be a novel series of ligand and should possess higher efficiency for Cu-based C–N coupling reactions due to the more stable structure and excellent solubility in water (Scheme 1). Herein, we wish to report 2-(hydrazinecarbonyl)pyridine *N*-oxide and its analogue as efficient N,O-bidentate ligands for the formation of copper-catalyzed C–N bonds in water.

In our initial experiment, 4-iodoanisole and imidazole were chosen as the model substrates to optimize reaction conditions including copper sources, ligands, bases, reaction temperature, and time, and the results are shown in Table 1.



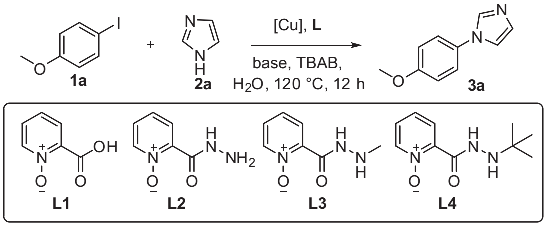
**Scheme 1.** Previous works and our work.

---

* Corresponding author. Tel.: +86 09932057213; fax: +86 13899508309.
*E-mail address:* cesxjw@gmail.com (J.-W. Xie).

http://dx.doi.org/10.1016/j.tetlet.2014.04.039
0040-4039/© 2013 Elsevier Ltd. All rights reserved.

**Table 1**
Screening reaction conditions for N-arylation of imidazole with 4-iodoanisole in water[a]



| Entry | [Cu] | Ligand | Base | Yield[b] (%) |
|---|---|---|---|---|
| 1 | CuI | **L1** | NaOH | 29 |
| 2 | CuI | **L2** | NaOH | 65 |
| 3 | CuI | **L3** | NaOH | 75 |
| 4 | CuI | **L4** | NaOH | 85 |
| 5 | CuI | — | NaOH | 8 |
| 6 | CuBr | **L4** | NaOH | 93 |
| 7 | CuCl | **L4** | NaOH | 94 |
| 8 | $Cu_2O$ | **L4** | NaOH | 81 |
| 9 | Cu | **L4** | NaOH | 95 |
| 10 | $CuSO_4$ | **L4** | NaOH | 49 |
| 11 | $Cu(OAc)_2$ | **L4** | NaOH | 71 |
| 12 | CuO | **L4** | NaOH | 60 |
| 13 | — | **L4** | NaOH | 0 |
| 14 | Cu | **L4** | KOH | 97 |
| 15 | Cu | **L4** | $K_2CO_3$ | 76 |
| 16 | Cu | **L4** | $K_3PO_4$ | 72 |
| 17 | Cu | **L4** | $Cs_2CO_3$ | 67 |
| 18 | Cu | **L4** | KOH | 27[c] |
| 19 | Cu | **L4** | KOH | 69[d] |

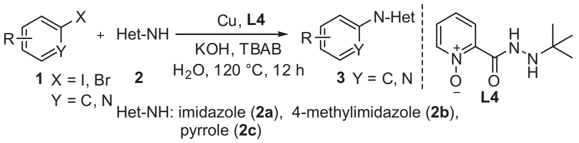
[a] Reaction conditions: 4-iodoanisole (0.5 mmol), imidazole (0.75 mmol), [Cu] (10 mol %), L (20 mol %), TBAB (30 mol %), base (1 mmol), solvent (1 mL), 120 °C, 12 h.

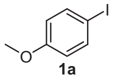
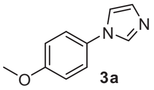
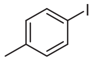
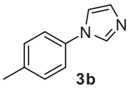
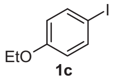
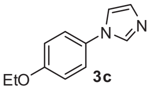
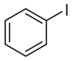
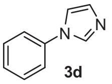
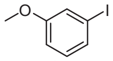
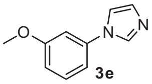
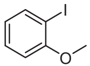
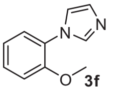
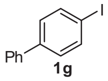
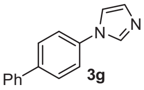
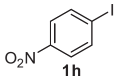
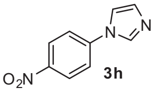
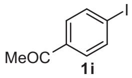
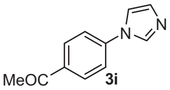
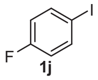
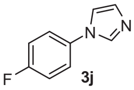
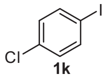
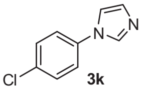
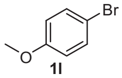
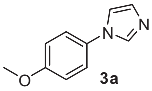
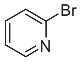
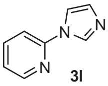
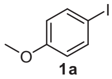
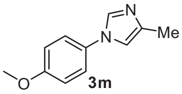
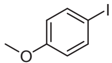
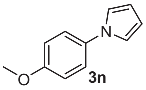
[b] Isolated yield.

[c] Cu (5 mol %), **L4** (10 mol %).

[d] Reaction temperature: 100 °C.

**Table 2**
Cu powder-catalyzed N-arylation of imidazoles with aryl halides using 2-(2-*tert*-butylhydrazinecarbonyl)pyridine *N*-oxide as ligand in water[a]



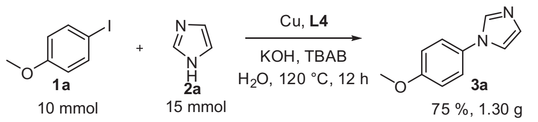
| Entry | ArX | Het-NH | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  **1a** | **2a** |  **3a** | 97 |
| 2 |  **1b** | **2a** |  **3b** | 70 |
| 3 |  **1c** | **2a** |  **3c** | 80 |
| 4 |  **1d** | **2a** |  **3d** | 75 |
| 5 |  **1e** | **2a** |  **3e** | 86 |
| 6 |  **1f** | **2a** |  **3f** | 44 |
| 7 |  **1g** | **2a** |  **3g** | 75 |
| 8 |  **1h** | **2a** |  **3h** | 60 |
| 9 |  **1i** | **2a** |  **3i** | 60 |
| 10 |  **1j** | **2a** |  **3j** | 73 |
| 11 |  **1k** | **2a** |  **3k** | 72 |
| 12 |  **1l** | **2a** |  **3a** | 32 |
| 13 |  **1m** | **2a** |  **3l** | 75 |
| 14 |  **1a** | **2b** |  **3m** | 76 |
| 15 |  **1a** | **2c** |  **3n** | 74 |

[a] Reaction conditions: ArX (0.5 mmol), Het-NH (0.75 mmol), Cu (0.05 mmol), **L4** (0.1 mmol), KOH (1 mmol), TBAB (0.15 mmol), $H_2O$ (1 mL).[9]

[b] Isolated yield.

As expected, the three 2-(hydrazinecarbonyl)pyridine *N*-oxides exhibited high catalytic activities. Surprisingly, the coupling product was obtained in 85% yield when CuI and sterically hindered **L4** were used as the catalyst and ligand (entries 1–4). Only a small amount of the target product formed without ligand (entry 5). With the favorable ligand in hand, we next screened the copper sources, and the preliminary results showed that copper reagents such as CuBr, CuCl, and Cu powder, combined with **L4** afforded the *N*-arylated products in excellent yields (entries 6–12). Since CuBr and CuCl are more expensive and oxidate easily, the most efficient, cheap, and air-stable Cu powder was selected as the catalyst. To the best of our knowledge, there are only a few examples for Cu(0)-catalyzed C–N coupling reaction.[7h,8] Control experiment conducted in the absence of catalyst from the reaction mixture resulted in no product (entry 13). Investigation of a variety of bases, including KOH, $K_2CO_3$, $K_3PO_4$, and $Cs_2CO_3$, indicated KOH to be the best one in 97% yield (entries 14–17). Decreasing the catalyst loading or shorter the reaction time all resulted lower yields (entries 18 and 19). In summary, the optimal conditions for this cross-coupling in water consist of the combination of Cu powder (10 mol %), **L4** (20 mol %), $(n\text{-Bu})_4NBr$ (TBAB) (30 mol %), and KOH (2 equiv) at 120 °C for 12 h without protection of inert atmosphere.

The scope of the procedure with respect to other substrates was studied (Table 2). Imidazole could be cross-coupled with most of aryl iodides to provide good to excellent yields. Electron-donating groups seemed to be a little beneficial for the catalytic system. Sterically hindered substrates declined the effectiveness of the reaction; *ortho*-subsituted aryl halide gave relatively lower yields than their *para*- and *meta*-isomer (entries 6 vs 1 and 5). Extension of this process to aryl bromide substrates has yielded promising results (entries 12 and 13). We were pleased to find that the arylation reactions also proceed with 4-methylimidazole and pyrrole in 76% and 74% yields under standard conditions (entries 14 and 15).



**Scheme 2.** Large-scale reaction of N-arylation of imidazole with 4-iodoanisole in water.

In order to make it to advance, we carried out the reaction on a large scale by taking 10 mmol of 4-iodoanisole and 15 mmol of imidazole in 10 mL of $H_2O$ at 120 °C for 12 h. The reaction proceeded without any difficulty to obtain good yields of *N*-aryl product (Scheme 2).

In conclusion, we have established a simple, environmentally friendly protocol for the N-arylation of imidazoles with aryl iodides and bromides promoted by copper powder/2-(2-*tert*-butylhydrazine-carbonyl)pyridine N-oxide catalytic system in water. The convenient operation, stable and inexpensive catalyst, and environmental friendliness, in combination with the efficient process for large scale preparation, render this method viable for use in both laboratory research and large industrial scales. Further investigation to broaden the scope of this catalytic system to other coupling reaction is currently ongoing in this laboratory.

## Acknowledgments

This work was supported by the National Basic Research Program of China (973 Program, No. 2012CB722603), the NSFC (No. 21103114), the Ministry of Education Innovation Team (No. IRT1161) and the Outstanding Youth Project of Shihezi University (2012ZRKXYQ-YD02, KF201303).

## Supplementary data

Supplementary data (experimental procedures and compound characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.039.

## References and notes

1. (a) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451; (b) Luca, L. D. *Curr. Med. Chem.* **2006**, *13*, 1; (c) Kison, C.; Opatz, T. *Chem. Eur. J.* **2009**, *4*, 843; (d) Gao, H.; Shreeve, J. M. *Chem. Rev.* **2011**, *111*, 7377.
2. (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400; (b) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.; Wiley-VCH: Weinheim, 2004.
3. (a) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684; (b) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578; (c) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78.
4. (a) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Talliefer, M. *Eur. J. Org. Chem.* **2004**, *4*, 695; (b) Monnier, F.; Taillefer, M. *Angew. Chem.* **2008**, *120*, 3140.
5. For some selected reviews: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400; (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428; (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337; (d) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450; (e) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954; (f) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096.
6. Carril, M.; SanMartin, R.; Domínguez, E. *Chem. Soc. Rev.* **2008**, *37*, 639.
7. For some selected examples: (a) Liang, L.; Li, Z.; Zhou, X. *Org. Lett.* **2009**, *11*, 3294; (b) Wang, Y.; Wu, Z.; Wang, L.; Li, Z.; Zhou, X. *Chem. Eur. J.* **2009**, *15*, 8971; (c) Xie, J.; Zhu, X.; Huang, M.; Meng, F.; Chen, W.; Wan, Y. *Eur. J. Org. Chem.* **2010**, 3219; (d) Li, X.; Yang, D.; Jiang, Y.; Fu, H. *Green Chem.* **2010**, *12*, 1097; (e) Li, Y.; Zhu, X.; Meng, F.; Wan, Y. *Tetrahedron* **2011**, *67*, 5450; (f) Thakur, K. G.; Ganapathy, D.; Sekar, G. *Chem. Commun.* **2011**, *47*, 5076–5078; (g) Wang, D.; Zhang, F.; Kuang, D.; Yu, J.; Li, J. *Green Chem.* **2012**, *14*, 1268; (h) Yang, Q.; Wang, Y.; Lin, D.; Zhang, M. *Tetrahedron Lett.* **2013**, *54*, 1994; (i) Yang, B.; Liao, L.; Zeng, Y.; Zhu, X.; Wan, Y. *Catal. Commun.* **2014**, *45*, 100.
8. (a) Zhu, R.; Xing, L.; Wang, X.; Cheng, C.; Su, D.; Hu, Y. *Adv. Synth. Catal.* **2008**, *350*, 1253; (b) Jiao, J.; Zhang, X.-R.; Chang, N.; Wang, J.; Wei, J.-F.; Shi, X.-Y.; Chen, Z.-G. *J. Org. Chem.* **2011**, *76*, 1180; (c) Audisio, D.; Messaoudi, S.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *J. Org. Chem.* **2011**, *76*, 4995; (d) Kidwai, M.; Mishra, N. K.; Bhardwaj, S.; Jahan, A.; Kumar, A.; Mozumdar, S. *ChemCatChem* **2010**, *2*, 1312.
9. *Typical experimental procedure:* Cu (0.05 mmol), **L4** (0.1 mmol), aryl halides (0.5 mmol), imidazoles (0.75 mmol), KOH (1 mmol), TBAB (0.15 mol), and $H_2O$ (1 mL) were added to a 10 mL sealed tube. The reaction mixture was reacted at 120 °C in a preheated oil bath for 12 h. The reaction mixture was cooled to room temperature, diluted with 10 mL $H_2O$, and then the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with water and brine, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatograph on silica gel (ethyl acetate/petroleum ether, 2:1 to pure ethyl acetate) to afford the target products.